POLY(ADP-RIBOSE)POLYMERASE INHIBITOR

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INPADOC Patentfamilie anzeigen

Liste der Anführungen anzeigen

Datenfehler hier melden

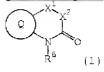
Zusammenfassung von **JP2001302515**

PROBLEM TO BE SOLVED: To provide a compound effective as a medicament for the therapy or prophylaxis of disease caused by the sthenia of poly(ADP-ribose)polymerase. SOLUTION: A poly(ADP-ribose)polymerase inhibitor comprises a compound represented by formula (1) [wherein -X1-X2- is a group represented by the formula -C(=O)-N(R7)- or -C(R8)=N-, or the like; R7 is H, a substituted or unsubstituted alkyl group, or the like; R8 is a substituted or unsubstituted alkyl group, or the like; ring Q is a group represented by the formula (2) to (4); and R1 to R6 are each H, a substituted or unsubstituted alkyl group, or the like] or a prodrug thereof, or at least one of their medicinally permissible salts.

DETAILED DESCRIPTION

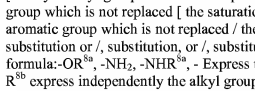
[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the compound which has poly (ADP-ribose) polymerase (PARP alias: poly (ADP-ribose) synthetase) inhibitory action. The disease to which the compound which has PARP inhibitory action originates in PARP activity sthenia, for example, a cerebral ischemic insult (for example, the sequela (the obstacles (for example, dyskinesia etc.) encountered as a sequela after the obstacle accompanying cerebral apoplexy and cerebral apoplexy are included) after cerebral apoplexy and cerebral apoplexy.) neurodegenerative diseases (for example, Parkinson's disease and an Alzheimer disease.), such as cerebral edema Cerebral contusion, head injury, spine damage, diabetes mellitus, such as Huntington's chorea, The organ derangement by ischemic heart disease (for example, myocardial infarction, angina pectoris, arrhythmia, etc.), the ischemia, or ischemia reperfusion. (For example, the obstacle etc. which are produced by surgical procedures, such as a myocardial ischemia reperfusion obstacle, acute renal failure, renal ischemia, an organ transplantation, and endermic coronary artery plastic operation), Inflammation (for example, arthritis, rheumatoid arthritis, septicemia), inflammatory enteritis. (For example, colitis, Crohn's disease, etc.), cancers, cachexia (cachexia), A renal damage, osteoporosis, an acute pain, and a chronic pain (for example, neurogenic pain etc.), Septicemia (for example, endotoxin shock etc.), skeletal muscle degeneration, myotrophia dystonica, macular degeneration Change of the gene expression of aging of the skin, aging of an ischemia-retinae obstacle and an immune system, AIDS, and an aging cell, retinitis pigmentosa, It is useful as a remedy or preventive medicines, such as a cell damage by a carcinostatic substance (for example, alkylating agents, such as nitrosourea). Especially The sequela after a cerebral ischemic insult, cerebral apoplexy, and cerebral apoplexy, the cerebral edema, a neurodegenerative disease, Parkinson's disease, an Alzheimer disease, Huntington's chorea, cerebral contusion, Head injury, spine damage, diabetes mellitus, ischemic heart disease, myocardial infarction, a myocardial ischemia reperfusion obstacle, Aging of angina pectoris, arrhythmia, arthritis, rheumatoid arthritis, inflammatory enteritis, septicemia, cancer, the cell damage by a carcinostatic substance, and the skin, an ischemia-retinae obstacle, macular degeneration It is useful as a remedy or preventive medicines, such as retinitis pigmentosa.
[0002]
[Description of the Prior Art]As a compound which has poly (ADP-ribose) polymerase inhibitory action, For example, a dihydroiso kino linon derivative and an isokino linon derivative (for example) [Anti-cancer Drug Design (1991) and] To 7,107-117, a statement, a bis-benzamide derivative (for example, the [international publication (WO)] the No. 99/47494 gazette statement), A tetracyclic compound (for example, the [international publication (WO)] the No. 99/11645 gazette statement) etc. are mentioned, In J.Biol.Chem. (1992), 267 (3), and 1569-1575 and the international publication (WO) of[99th] No. 11624 gazette, the poly (ADP-ribose) polymerase inhibitory action of the compound which has

various skeletons is indicated.
[0003]
[Problem(s) to be Solved by the Invention]In recent years, although PARP inhibitor of various chemical structure as mentioned above is found out, the invention of the compound which has a stronger operation, and few side effects, and development are desired.
[0004]
[Means for Solving the Problem]A result wholeheartedly examined in order that this invention persons might attain an aforementioned problem, It found out having the poly (ADP-ribose) polymerase inhibitory action excellent in a salt (it may be called this invention compound for short if needed below) permitted as a compound expressed with a general formula (1), its prodrug, or those medicines. This invention relates to the following.
[1]Formula (1)
[Formula 5]



(1)

-X^1-X^2- among [type Formula:-C(=O)-N(R^7)-, - Express the basis expressed with CH(R^8)-N(R^7)- or -C(R^8)=N-, R^7 The alkenyl group which is not replaced [the alkyl group which is not replaced / a hydrogen atom, substitution, or /, substitution, or], The cycloalkyl group which is not replaced [the alkynyl group which is not replaced / substitution or /, substitution or], The arylated alkyl group which is not replaced [the cycloalkyl alkyl group which is not replaced / substitution or /, substitution or], The saturation heterocycle group which is not replaced [the aromatic group which is not replaced / substitution or /, substitution or], R^8 the acyl group which is not replaced [substitution or] Or the alkyl group which is not replaced [substitution or], The alkynyl group which is not replaced [the alkenyl group which is not replaced / substitution or /, substitution or], The cycloalkyl alkyl group which is not replaced [the cycloalkyl group which is not replaced / substitution or /, substitution or], The acyl group which is not replaced [the saturation heterocycle group which is not replaced / the aromatic group which is not replaced / the arylated alkyl group which is not replaced / substitution or /, substitution, or /, substitution, or /, substitution, or], a halogen atom or formula:-OR^{8a}, -NH_2, -NHR^{8a}, - Express the basis expressed with $NR^{8a}R^{8b}$ or -SR^{8a} (R^{8a} and R^{8b} express independently the alkyl group which is not replaced [substitution or], respectively). The ring Q is a formula. : [Formula 6]



または

It comes out and a basis expressed is expressed. R^1, R^2, R^3, and R^4, Independently, respectively An alkenyl group which is not replaced [an alkyl group which is not replaced / a hydrogen atom substitution, or /, substitution, or], A cycloalkyl group which is not replaced [an alkynyl group which is not replaced / substitution or /, substitution or], An arylated alkyl group which is not replaced [a cycloalkyl alkyl group which is not replaced / substitution or /, substitution or], A saturation heterocycle group which is not replaced [an aromatic group which is not replaced / substitution or /, substitution or], An acyl group which is not replaced [substitution or], a halogen atom, a nitro group, or formula:-OR^{1a}, - Express a basis expressed with $NR^{1a}R^{1b}$ or -SR^{1a} (R^{1a} and R^{1b} express independently an alkyl group which is not replaced [a hydrogen atom, substitution, or], respectively). Independently R^5 and R^6, respectively A hydrogen atom, An alkenyl group which is not replaced [an alkyl group which

is not replaced / substitution or /, substitution or], A cycloalkyl group which is not replaced [an alkynyl group which is not replaced / substitution or /, substitution or], An acyl group which is not replaced [a saturation heterocycle group which is not replaced / an aromatic group which is not replaced / an arylated alkyl group which is not replaced / a cycloalkyl alkyl group which is not replaced / substitution or /, substitution, or /, substitution, or /, substitution, or /, substitution, or] is expressed. However, the ring Q is a formula. : [Formula 7]

It comes out, and in being a basis expressed, it excludes a case where R^4 and R^6 are hydrogen atoms simultaneously. Poly (ADP-ribose) polymerase inhibitor containing a salt permitted as a compound expressed with], its prodrug, or those medicines.

[2]The ring Q is a formula. : [Formula 8]

It is a basis come out of and expressed. [1]Poly (ADP-ribose) polymerase inhibitor of a statement.

[3]. [whether R^7 is an alkyl group which is not replaced / a hydrogen atom, substitution, or / and] Or R^8 is an alkyl group which is not replaced [substitution or], and R^6 is a cycloalkyl alkyl group which is not replaced [the cycloalkyl group which is not replaced / the alkyl group which is not replaced / a hydrogen atom, substitution, or /, substitution, or /, substitution, or], [1]or[2]Poly (ADP-ribose) polymerase inhibitor of a statement.

[4]A sequela after a cerebral ischemic insult, cerebral apoplexy, and cerebral apoplexy, cerebral edema, a neurodegenerative disease, Parkinson's disease, An Alzheimer disease, Huntington's chorea, cerebral contusion, head injury, spine damage, Aging of diabetes mellitus, ischemic heart disease, myocardial infarction, a myocardial ischemia reperfusion obstacle, angina pectoris, arrhythmia, arthritis, rheumatoid arthritis, inflammatory enteritis, septicemia, cancer, a cell damage by a carcinostatic substance, and the skin, an ischemia-retinae obstacle, macular degeneration Or it is a treating agent or preventive of retinitis pigmentosa, [1]-Poly (ADP-ribose) polymerase inhibitor given in either of [3].

[0005]Various kinds of bases in this invention are explained below. Especially, as long as there are no directions, the following explanation corresponds, also when each bases are a part of other bases.

[0006]As an alkyl group, straight chains, such as methyl, ethyl, propyl, 2-propyl, butyl, 2-butyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, hexyl, heptyl, and octyl, or the branched eight or less-carbon atom alkyl group is mentioned, for example.

[0007]As an alkenyl group, six or less alkenyl group with a numbers [, such as vinyl, allyl, propenyl, 2-propenyl, butenyl, pentenyl and hexenyl,] of carbon atoms is mentioned, for example.

[0008]As an alkynyl group, six or less alkynyl group with a numbers [, such as ethynyl, propargyl, butynyl, and pentynyl,] of carbon atoms is mentioned, for example.

[0009]As a cycloalkyl group, 3 - 8 membered-ring cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl one, are mentioned, for example.

[0010]As a cycloalkenyl group, a cycloalkenyl group which has one double bond of three to 8 membered-rings, such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl,

2-cyclohexenyl, and 3-cyclohexenyl, for example is mentioned.
[0011]As a cycloalkyl alkyl group, a basis which said cycloalkyl group replaced, for example by said alkyl group is mentioned.
[0012]An aryl group and a heteroaryl group are mentioned as an aromatic group. As an aryl group, ten or less-carbon atom aryl groups, such as a phenyl group and a naphthyl group, are mentioned, for example. A basis 5 which contains 1-2 nitrogen atoms as a heteroaryl group, for example - 6 member monocyclic, A basis 5 which contains [a nitrogen atom] one piece or one sulfur atom for 1-2 pieces and an oxygen atom - 6 member monocyclic, Including a 5 member monocyclic basis containing one piece or one sulfur atom and 1-4 nitrogen atoms, an oxygen atom is mentioned by 2 cyclic basis etc. which six membered-rings, 5, or 6 membered-rings condensed, and it specifically, For example, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-thienyl, 3-thienyl, 3-oxadiazolyl, 2-imidazolyl, 2-thiazolyl, 3-isothiazolyl, 2-oxazolyl, 3-isoxazolyl, 2-furil, 3-furil, 3-pyrrolyl, 2-quinolyl, 8-quinolyl, 2-chinac-cortex ZORINIRU, 8-Puri Nils, etc. are mentioned.
[0013]As a halogen atom, iodine, fluoride, chlorine, and a bromine atom are mentioned, for example.
[0014]As an arylated alkyl group, an alkyl group replaced by said aryl group is mentioned.
[0015]A basis of six to 8 membered-ring which has one nitrogen atom and one oxygen atom, such as a basis of six to 8 membered-ring which has two nitrogen atoms, such as a basis of five to 8 membered-ring which has one nitrogen atom, such as 1-piperidinyl and 1-pyrrolidinyl, for example, and 1-piperazinyl, as a saturation heterocycle group, and morpholino, is mentioned.
[0016]As a substituent of a saturation heterocycle group and a saturation heterocycle carbonyl group, a hydroxyl group, a carboxyl group, a halogen atom, an alkoxycarbonyl group, etc. are mentioned as a substituent on a carbon atom, and an alkyl group, an alkoxycarbonyl group, etc. are mentioned as a substituent on a nitrogen atom.
[0017]As an acyl group, an alkanoyl group with 2-6 carbon atoms, such as a formyl group, for example, acetyl, and propanoly, For example, cyclopropane carbonyl, cyclobutane carbonyl, cyclopentane carbonyl, A cycloalkane carbonyl group with 4-7 carbon atoms, such as cyclohexane carbonyl, For example, a cycloalkene carbonyl group with 3-6 carbon atoms, such as cyclopentene carbonyl and cyclohexene carbonyl, For example, an aroyl group with 6-10 carbon atoms, such as benzoyl, toluoyl, and naphthoyl, For example, nitrogen atoms, such as 2-piperidine carbonyl and 3-morpholine carbonyl, A saturation heterocycle carbonyl group which has the saturation heterocycle of 5 or 6 members containing 1-2 hetero atoms chosen from an oxygen atom and a sulfur atom, For example, a complex aromatic acyl group etc. which have a complex aromatic ring of 5 or 6 members containing 1-2 hetero atoms chosen from nitrogen atoms, such as 2-furoyl, 3-furoyl, 2-TENOIRU, 3-TENOIRU, nicotinoyl, and isonicotinoyl, an oxygen atom, and a sulfur atom are mentioned.
[0018]An alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, a cycloalkyl alkyl group, An alkanoyl group, a cycloalkane carbonyl group, and a cycloalkene carbonyl group, and a substituent of an alkyl part of an arylated alkyl group -- a piece -- or, or it differing, and there being more than one and as a substituent, For example, a halogen atom, a cyano group, a phenoxy group, a benzyloxy group, A trifluoromethyl group, a hydroxyl group, a lower alkoxy group, a low-grade alkanoloxy group, An amino group, a mono- lower alkylamino group, a JI lower alkylamino group, a carbamoyl group, A low-grade alkylamino carbonyl group, a JI low-grade alkylamino carbonyl group, A low-grade alkoxycarbonylamino group, a carboxyl group, a low-grade alkoxycarbonyl group, A low-grade alkylthio group and low-grade alkyl sulfinyl group, a low-grade alkyl sulfonyl group, a low-grade alkanoyl amino group, a low-grade alkyl sulfonamide group, a Tori low-grade alkyl silyl group, a phthalimide group, a heteroaryl group, or a saturation heterocycle group is mentioned.

[0019]As a substituent of aryl portions of an aromatic group, an aroyl group, a complex aromatic acyl group, and an arylated alkyl group, a piece -- or the same -- or -- it may differ and there may be more than one -- for example, a halogen atom. A cyano group, a trifluoromethyl group, a nitro group, a hydroxyl group, a methylenedioxy group, A low-grade alkyl group, a lower alkoxy group, a benzyloxy group, a low-grade alkanoloxy group, An amino group, a mono- lower alkylamino group, a JI lower alkylamino group, a carbamoyl group, A low-grade alkylamino carbonyl group, a JI low-grade alkylamino carbonyl group, A carboxyl group, low-grade alkoxycarbonyl group, low-grade alkylthio group, and low-grade alkyl sulfinyl group, a low-grade alkyl sulfonyl group, a low-grade alkanoyl amino group, or a low-grade alkyl sulfonamide group is mentioned.
[0020]That it is low-grade means that an alkylated site of the substituent concerned is a low-grade alkyl group, and four or less-carbon atom bases, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, and tert-butyl, are mentioned as such a low-grade alkyl group, for example.
[0021]A compound expressed with a general formula (1) is a publicly known compound, or can be compounded by a publicly known method from a publicly known compound. For example, the ring Q is a formula. : [Formula 9]

As for the compound come out of and expressed, the ring Q is a formula to the publication-of-patent-applications Showa 51 No. 25193 gazette per year, a U.S. Pat. No. 3,950,526 specification, etc. : [Formula 10]

As for the compound come out of and expressed, the ring Q is a formula to the Europe (EP) patent No. 736569 public presentation (A) gazette etc. : [Formula 11]

Come out and a compound expressed The 1459 - 1467th page with a chemical and Pharmaceutical Bure Tan of volume [22nd], It can obtain by a method indicated in 1974 (Chem.Pharm. Bull (1974), 22 (7), 1459-67) etc., respectively.
[0022]That in which a compound expressed with a formula (1) has an optical unsymmetrical center is also contained, therefore these can be obtained with an optical activity type, when a charge of a start material of optical activity is used as racemate. If required, obtained racemate can be divided into those optical antipodes by a publicly known method physically or chemically. Preferably, diastereomer is formed from racemate by the reaction using an optical activity resolving agent. Diastereomer of a different form can be divided, for example by publicly known methods, such as fractional crystallization.
[0023]As a "prodrug", it is hydrolyzed easily in the living body, and what reproduces a compound of a formula (1) is mentioned, For example, if it is a compound which has a carboxyl group, a compound in which the carboxyl group turned into an alkoxycarbonyl group, a compound used as an alkylthio carbonyl group, or a compound used as an

alkylamino carbonyl group will be mentioned. A compound which the amino group was replaced by an alkanoyl group, and became an alkanoyl amino group when it was a compound which has an amino group, for example, A compound which was replaced by alkoxycarbonyl group and became an alkoxycarbonylamino group, a compound used as an acyloxy methylamino group, or a compound used as hydroxylamine is mentioned. For example, if it is a compound which has a hydroxyl group, a compound which the hydroxyl group was replaced by said acyl group, and became an acyloxy group, a compound used as phosphoric ester, or a compound used as an acyloxy methyloxy group will be mentioned. Said alkyl group may be mentioned as an alkyl part of a basis used for these prodrug-ization, and the alkyl group may be replaced (for example, alkoxy group with 1-6 carbon atoms, etc.). If a carboxyl group takes a compound used as an alkoxycarbonyl group for an example as a desirable example, for example, Low-grade (for example, carbon numbers 1-6) alkoxy carbonyls, such as carbomethoxy and ethoxycarbonyl, Methoxy carbomethoxy and ethoxycarbomethoxy, 2-methoxyethoxy carbonyl, Low-grade (for example, carbon numbers 1-6) alkoxy carbonyl replaced by alkoxy groups, such as 2-methoxyethoxy carbomethoxy and PIBARO yloxy carbomethoxy, is mentioned.

[0024]A compound expressed with a formula (1) or its prodrug can be made into a salt permitted as medicine if needed. As such a salt, for example Salt; formic acid with mineral acid, such as chloride, hydrobromic acid, sulfuric acid, and phosphoric acid, Acetic acid, fumaric acid, maleic acid, oxalic acid, citrate, malic acid, tartaric acid, A salt with organic carboxylic acid, such as aspartic acid and glutamic acid; Methanesulfonic acid, Benzenesulfonic acid, p-toluenesulfonic acid, hydroxybenzenesulfonic acid, A salt with sulfonic acid, such as dihydroxybenzenesulfonic acid; It reaches, For example, alkali metal salt, such as sodium salt and potassium salt; Calcium salt, alkaline-earth-metal-salt [, such as magnesium salt,]; -- ammonium salt; -- a triethylamine salt, a pyridine salt, a picoline salt, ethanolamine salt, a dicyclohexylamine salt, a salt with N,N'-dibenzylethylenediamine, etc. are mentioned. A salt permitted as a compound expressed with a formula (1), its prodrug, or those medicines may be those anhydrides, a hydrate, or solvate.

[0025]In using these as medicine, an oral target or a parenteral target can be medicated with this invention compound. That is, parenteral administration of what could be prescribed for the patient in taking orally by pharmaceutical forms, such as a dosage form usually used, for example, powder, granulation, a tablet, a capsule, syrups, and suspension, or was made into a pharmaceutical form of the solution, an emulsion, and suspension, for example can be carried out with a mold of injection. Rectum administration can also be carried out with a mold of suppositories. The suitable aforementioned administration pharmaceutical form can be manufactured by, for example, blending this invention compound with the usual carrier permitted, an allocated type agent, a binding material, stabilizer, and a diluent. When using with an injections type, a buffer, a solubilizing agent, and an isotonic agent which are permitted can also be added, for example. Although a dose and frequency of administration change with an object disease, condition, age, weight, and dosage forms, they can usually prescribe preferably 1-200 mg of 0.1-2000 mg [per day] for the patient in 1 time or several steps (for example, 2 to 4 times) to an adult, for example.

[0026]

[Example]Although the example of an examination of this invention is shown below, this invention is not limited to this from the first. A compound name does not necessarily follow an IUPAC nomenclature.

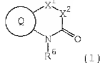
[0027]The example of an examination [A reagent and equipment]

- DNA (finishing [ultrasonication]) (Nacalai Tesque), nicotinamide adenine dinucleotide (NAD: Nacalai Tesque), and [^{3}H] NAD (adenine 2 and [8-^{3}H]-NAD) (NEN(registered trademark) Life.) Science Products, Inc. (U.S.), and specific activity 1402 GBq/mmol and PARP (the Homo sapiens PARP recombination object.) 660 units / mg (Trevigen, Inc.

(U.S.)), benzamide (Wako Pure Chemical Industries, Ltd.), and 96 well plate (a round-bottom perfect plate.) The product made from polypropylene. (CORNING.) Costar. (The U.S.) The glass fiber filter for -96 well plates: Pudding TEDDO Filter mat B (double thickness, 90x120 mm) (PerkinElmer, Inc. (U.S.)) and a solid scintillator sheet :. [MeltiLex] (Registered trademark) The sample back for enclosure of A and (PerkinElmer (73x109 mm - 4 g / sheet), Inc. (U.S.)) a filter + scintillator (PerkinElmer, Inc. (U.S.)) [0028][Test method] Buffer solution (50 mM Tris-HCl (pH 8.0) / 25mM $MgCl_2$ solution) was used for preparation of each solution. On 96 hole round-bottom plate made from polypropylene, sample compound solution 20mul / well, 1microM containing 10 microg/ml DNA [^{3}H] NAD(specific activity 7 kBq/ml)30microl / well, 4 units / ml PARP (6 microg/(ml)) solution 50mul / well was added one by one, and the reaction was advanced at the room temperature for 1.5 hours (each reagent last concentration in reaction mixture). DNA: 3 microg [ml] /, [^{3}H] NAD : 0.3microM/specific activity 2.1 kBq/ml, and PARP:2 unit / ml (3 microg/(ml)). Carry out 9microl / well addition of the benzamide of 24mM (after-addition 2 mM), it was made to stop, and the reaction collected PARP(s) in reaction mixture on the glass fiber filter for plates by the cell harvester (HARVESTER 96 (registered trademark), TOMTEC Inc. (U.S.)). The glass fiber filter washed each well of the plate for ethanol 4 times by ethanol 80% after through and PARP recovery 80% just before PARP recovery, and the penetrant remover also let it pass to the glass fiber filter. With the microwave oven, a glass fiber filter is heated for 3 to 4 minutes, and was dried, and two solid scintillator sheets were piled up, it put in the sample back, and heat sealing enclosed. Place this on about 50 ** heater, and the thermal melting solution of the scintillator is carried out, After making a filter permeate, return to a room temperature and at the counter for plates (1450 MicroBeta (registered trademark) TriLux, PerkinElmer, Inc. (U.S.)). The count (cpm) of [^{3}H] in poly (ADP-ribose) added to PARP was measured (10 minute / plate).
[0029]The inhibition rate to PARP activity was computed using the following formulas.
An inhibition rate. (%) =[1-. Count (cpm)-background count (cpm))/(count (cpm)-background count (cpm) of compound non-adding well)]x100 of (compound addition well (background count = count (cpm) of a compound, and PARP a non-adding well)
About each sample compound, the inhibition rate was measured by n= 2 and IC_{50} value was computed.
[0030][Test result]
1-methyl-2,4-(1H,3H)-quinazoline dione : IC_{50}=0.44microM, 1-(cyclopropyl methyl)-2,4-(1H,3H)-quinazoline dione : IC_{50}=0.16microM, 4-methyl-2(1H)-KINAZO linon : IC_{50}=2.2microM, 1-ethyl-1H-pyrrolo [2,3-] [d] pyrimidine 2,4(3H,7H)-dione: IC_{50}=0.31microM and 1-ethyl-6,7-dihydro-1H-pyrrolo [2,3-] [d] pyrimidine 2,4(3H,5H)-dione:IC_{50}=1.2microM

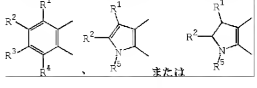
CLAIMS

[Claim(s)]
[Claim 1]A formula (1)
[Formula 1]



(1)

-X^1-X^2- among [type Formula:-C(=O)-N(R^7)-, - Express the basis expressed with CH(R^8)-N(R^7)- or -C(R^8)=N-, R^7 The alkenyl group which is not replaced [the alkyl group which is not replaced / a hydrogen atom, substitution, or /, substitution, or], The cycloalkyl group which is not replaced [the alkynyl group which is not replaced / substitution or /, substitution or], The arylated alkyl group which is not replaced [the cycloalkyl alkyl group which is not replaced / substitution or /, substitution or], The saturation heterocycle group which is not replaced [the aromatic group which is not replaced / substitution or /, substitution or], R^8 the acyl group which is not replaced [substitution or] Or the alkyl group which is not replaced [substitution or], The alkynyl group which is not replaced [the alkenyl group which is not replaced / substitution or /, substitution or], The cycloalkyl alkyl group which is not replaced [the cycloalkyl group which is not replaced / substitution or /, substitution or], The acyl group which is not replaced [the saturation heterocycle group which is not replaced / the aromatic group which is not replaced / the arylated alkyl group which is not replaced / substitution or /, substitution, or /, substitution, or /, substitution, or], a halogen atom or formula:-OR^{8a}, -NH_2, -NHR^{8a}, - Express the basis expressed with $NR^{8a}R^{8b}$ or -SR^{8a} (R^{8a} and R^{8b} express independently the alkyl group which is not replaced [substitution or], respectively). The ring Q is a formula. : [Formula 2]



または

It comes out and a basis expressed is expressed. R^1, R^2, R^3, and R^4, Independently, respectively An alkenyl group which is not replaced [an alkyl group which is not replaced / a hydrogen atom substitution, or /, substitution, or], A cycloalkyl group which is not replaced [an alkynyl group which is not replaced / substitution or /, substitution or], An arylated alkyl group which is not replaced [a cycloalkyl alkyl group which is not replaced / substitution or /, substitution or], A saturation heterocycle group which is not replaced [an aromatic group which is not replaced / substitution or /, substitution or], An acyl group which is not replaced [substitution or], a halogen atom, a nitro group, or formula:-OR^{1a}, - Express a basis expressed with $NR^{1a}R^{1b}$ or -SR^{1a} (R^{1a} and R^{1b} express independently an alkyl group which is not replaced [a hydrogen atom, substitution, or], respectively). Independently R^5 and R^6, respectively A hydrogen atom, An alkenyl group which is not replaced [an alkyl group which is not replaced / substitution or /, substitution or], A cycloalkyl group which is not replaced [an alkynyl group which is not replaced / substitution or /, substitution or], An acyl group which is not replaced [a saturation heterocycle group which is not replaced / an aromatic group which is not replaced / an arylated alkyl group which is not replaced / a cycloalkyl alkyl group which is not replaced / substitution or /, substitution, or /, substitution, or /, substitution, or /, substitution, or] is expressed. However, the ring Q is a formula. : [Formula 3]

It comes out, and in being a basis expressed, it excludes a case where R^4 and R^6 are hydrogen atoms simultaneously. Poly (ADP-ribose) polymerase inhibitor containing a salt permitted as a compound expressed with], its prodrug, or those medicines.
[Claim 2]The ring Q is a formula. : [Formula 4]

The poly (ADP-ribose) polymerase inhibitor according to claim 1 which is a basis come out of and expressed.
[Claim 3]. [whether R^7 is an alkyl group which is not replaced / a hydrogen atom, substitution, or / and] Or R^8 is an alkyl group which is not replaced [substitution or], The poly (ADP-ribose) polymerase inhibitor according to claim 1 or 2 whose R^6 is a cycloalkyl alkyl group which is not replaced [a cycloalkyl group which is not replaced / an alkyl group which is not replaced / a hydrogen atom, substitution, or /, substitution, or /, substitution, or].
[Claim 4]A sequela after a cerebral ischemic insult, cerebral apoplexy, and cerebral apoplexy, cerebral edema, a neurodegenerative disease, Parkinson's disease, An Alzheimer disease, Huntington's chorea, cerebral contusion, head injury, spine damage, Diabetes mellitus, ischemic heart disease, myocardial infarction, a myocardial ischemia reperfusion obstacle, angina pectoris, arrhythmia, Aging of arthritis, rheumatoid arthritis, inflammatory enteritis, septicemia, cancer, a cell damage by a carcinostatic substance, and the skin, an ischemia-retinae obstacle, macular degeneration Or the poly (ADP-ribose) polymerase inhibitor according to any one of claims 1 to 3 which is a treating agent or preventive of retinitis pigmentosa.

[Translation done.]